(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 June 2003 (19.06.2003)

PCT

(10) International Publication Number
WO 03/049720 A1

(51) International Patent Classification[7]: A61K 9/20, 9/127, 31/135, 31/415, 31/44

(21) International Application Number: PCT/US02/38376

(22) International Filing Date: 3 December 2002 (03.12.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/338,341 7 December 2001 (07.12.2001) US

(71) Applicant *(for all designated States except US)*: **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **MURRAY, Richard, K.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **YATES, John** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/049720 A1

(54) Title: COMBINATION THERAPY COMPRISING A CYCLOOYGENASE-2 INHIBITOR

(57) Abstract: The present invention encompasses a method and kit for treating a chronic cyclooxygenase-2 mediated disease or condition and reducing the risk of a thrombotic cardiovascular event in a human patient in need of such treatment and at risk of a thrombotic cardiovascular event comprising orally administering to said patient a cyclooxygenase-2 selective inhibitor on a once or twice daily basis in an amount effective to treat the cyclooxygenase-2 mediated disease or condition and orally administering to said patient aspirin once every two to seven days in an amount effective to reduce the risk of the thrombotic cardiovascular event while maintaining a high level of upper gastrointestinal safety and tolerability.

COMBINATION THERAPY COMPRISING A CYCLOOYGENASE-2 INHIBITOR

BACKGROUND OF THE INVENTION

Inhibitors of cyclooxygenase-2 are a sub-class of the class of drugs known as non-steroidal antiinflammatory drugs (NSAIDs). The NSAIDs are active in reducing the prostaglandin-induced pain and swelling associated with the inflammation process but are also active in affecting other prostaglandin-regulated processes not associated with the inflammation process. Thus, use of high doses of most common NSAIDs can produce severe side effects, including life threatening ulcers, that limit their therapeutic potential. An alternative to NSAIDs is the use of corticosteroids, which have even more drastic side effects, especially when long term therapy is involved.

Previous NSAIDs have been found to prevent the production of prostaglandin by inhibiting enzymes in the human arachidonic acid/prostaglandin pathway including the enzyme cyclooxygenase (COX). The recent discovery that there are two isoforms of the COX enzyme, the first, COX-1, being involved with physiological functions and the second, COX-2, being induced in inflamed tissue, has given rise to a new approach. While conventional NSAIDs block both forms of the enzyme, the identification of the inducible COX-2 enzyme associated with inflammation has provided a viable target of inhibition which more effectively reduces inflammation and produces fewer and less drastic side effects. Many compounds which have activity as COX-2 inhibitors have been identified, including rofecoxib (VIOXX®), etoricoxib (ARCOXIA™), celecoxib (CELEBREX®) and valdecoxib (BEXTRA™), and much research continues in this area.

Many patients with a chronic cyclooxygenase-2 mediated disease or condition are elderly and thus are at increased risk for thrombotic cardiovascular events, such as stroke, myocardial ischemia, myocardial infarction, angina pectoris, transient ischemic attack (TIA; amaurosis fugax), reversible ischemic neurologic deficits, and any similar thrombotic event in any vascular bed (splanchnic, renal, aortic, peripheral, etc.). Moreover, there is evidence that patients with chronic inflammatory conditions, such as rheumatoid arthritis and systemic lupus erythematosis are at increased risk for thrombotic cardiovascular events. Thus, it is

desirable that such patients receive appropriate antiplatelet therapy, such as aspirin, to reduce their risk of such events. However, very recent information from studies of the COX-2 selective inhibitors show that the incidence of gastric ulcer events in patients receiving both low-dose aspirin and the COX-2 selective inhibitor is similar to that seen with conventional NSAIDS that inhibit both COX-1 and COX-2. Also, some conventional NSAIDS, such as Naprosyn (naproxen sodium), when taken regularly, have been shown to have significant antiplatelet activity as well as efficacy in treating chronic cyclooxygenase-2 mediated diseases or conditions. Thus, the major advantage that COX-2 specific inhibitors have over NSAIDS may be substantially or completely offset by the concomitant use of aspirin.

The propensity of aspirin to induce GI ulcers and bleeding is known to be dose related. However, even doses as low as 30 to 50 mg/day have been reported to be associated with an increase in GI events (AJM 110 (1A) Patrono, 2001). Thus there is no proven effective dose of aspirin that inhibits thrombosis while having no impact on the GI mucosa. Some authors have advocated using less frequent than daily dosing as an approach to reducing the amount of aspirin given. However, there is no evidence to support that giving the same cumulative total dose on a less-than-daily basis is safer than receiving that dose once daily. Surprisingly, dosing with aspirin at a higher unit dose, but less frequently than daily, achieves substantially similar antiplatelet efficacy while having a markedly lower propensity to induce gastric or other upper gastrointestinal ulcers and bleeds. For example, aspirin 325 mg dosed every fourth day, either alone or in the presence of a COX-2 inhibitor, is associated with fewer gastric erosions or ulcers than 81 mg administered once daily. Even more surprisingly, at an even higher cumulative dose, a longer than one day interval between doses can be associated with a lower incidence of upper GI events. For example, aspirin 650 mg dosed every fourth day, either alone or in the presence of a COX-2 inhibitor, is associated with fewer gastric erosions or ulcers than 81 mg administered once daily, despite the doubling in cumulative dose. The mean life span of human platelets is approximately 10 days (Patronon et al. CHEST 1998; 114: 470S-488S) and the effects of aspirin on individual platelets is irreversible, so that 5 to 6 days following dosing with aspirin, approximately 50% of the platelets function normally.

Notwithstanding this surprising relationship between cumulative dose, unit dose and dosing interval, in general there is an inherent problem with administering doses of any drug less frequently than daily, unless the interval

coincides with a convenient calendar schedule, such as weekly, monthly or yearly. Thus, if a patient is asked, for example, to take a drug once every three days, he/she must remember to take the drug on Monday, Thursday, Sunday, Wednesday etc. Since the use of low-dose aspirin is for prevention of asymptomatic disease, the compliance problem is further compounded. Thus, is the absence of symptom relief associated with dosing, the majority of patients would be likely to become non-compliant within months of starting such a regimen.

In the current invention, aspirin is administered together with a COX-2 inhibitor leading to several advantages:

1) The less-than-daily frequency of administration of aspirin reduces the risk of GI ulcers and bleeds (which is otherwise particularly increased when both a COX-2 inhibitor and aspirin are administered on a daily basis) while providing substantial antiplatelet efficacy;

2) The COX-2 specific inhibitor provides symptom relief for the chronic cyclooxygenase-2 mediated disease or condition, such as chronic pain or arthritis;

3) Failure to remember to take the COX-2 specific inhibitor results in a return of symptoms, thus prompting the patient to take their dose; and

4) Coadministration of aspirin with the COX-2 specific inhibitor greatly increases convenience and improves compliance to the less-than-daily aspirin regimen.

Thus, the invention provides for a clearly superior profile than that hitherto obtainable in that it provides efficacy in treating chronic cyclooxygenase-2 mediated diseases or conditions, effectively inhibits platelets thus reducing the risk of thrombotic cardiovascular events and at the same time reduces the risk of GI ulceration or bleeding relative either to conventional NSAIDS or separate administration of a COX-2 inhibitor and low-dose daily aspirin, or than a NSAID plus ASA.

SUMMARY OF THE INVENTION

The present invention encompasses a method and kit for treating a chronic cyclooxygenase-2 mediated disease or condition and reducing the risk of a thrombotic cardiovascular event in a human patient in need of such treatment and at risk of a thrombotic cardiovascular event comprising orally administering to said patient a cyclooxygenase-2 selective inhibitor on a once or twice daily basis in an

amount effective to treat the cyclooxygenase-2 mediated disease or condition and orally administering to said patient aspirin once every two to seven days in an amount effective to reduce the risk of the thrombotic cardiovascular event while maintaining a high level of upper gastrointestinal safety and tolerability.

DETAILED DESCRIPTION OF THE INVENTION

The present invention encompasses a method and kit for treating a chronic cyclooxygenase-2 mediated disease or condition and reducing the risk of a thrombotic cardiovascular event in a human patient in need of such treatment and at risk of a thrombotic cardiovascular event comprising orally administering to said patient a cyclooxygenase-2 selective inhibitor on a once or twice daily basis in an amount effective to treat the cyclooxygenase-2 mediated disease or condition and orally administering to said patient aspirin once every two to seven days in an amount effective to reduce the risk of the thrombotic cardiovascular event while maintaining a high level of upper gastrointestinal safety and tolerability.

The invention encompasses a method for treating a chronic cyclooxygenase-2 mediated disease or condition and reducing the risk of a thrombotic cardiovascular event in a human patient in need of such treatment and at risk of a thrombotic cardiovascular event comprising orally administering to said patient a cyclooxygenase-2 selective inhibitor on a once or twice daily basis in an amount effective to treat the cyclooxygenase-2 mediated disease or condition and orally administering to said patient aspirin once every two to seven days in an amount effective to reduce the risk of the thrombotic cardiovascular event.

The term "treating a chronic cylcooxygenase-2 mediated disease or condition" means treating or preventing any chronic disease or condition that is advantageously treated or prevented by inhibiting the cyclooxygenase-2 enzyme. The term includes the relief of pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back pain, neck pain, dysmenorrhea, headache, migraine, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout, ankylosing spondylitis, bursitis, burns, injuries, and pain and inflammation following surgical procedures. In addition, such a compound may inhibit cellular neoplastic transformations and metastic tumor growth and hence can be used in the treatment of cancer. In addition, such a compound may inhibit the onset or progression of

Altzheimer's disease or cognitive impairment. The term also includes the treatment and/or prevention of cyclooxygenase-mediated proliferative disorders such as may occur in diabetic retinopathy and tumor angiogenesis. The term "treating" encompasses not only treating a patient to relieve the patient of the signs and symptoms of the disease or condition but also prophylactically treating an asymptomatic patient to prevent the onset or progression of the disease or condition.

A "thrombotic cardiovascular event" is defined as any sudden event of a type known to be caused by platelet aggregation, thrombosis, and subsequent ischemic clinical events, including thrombotic or thromboembolic stroke, myocardial ischemia, myocardial infarction, angina pectoris, transient ischemic attack (TIA; amaurosis fugax), reversible ischemic neurologic deficits, and any similar thrombotic event in any vascular bed (splanchnic, renal, aortic, peripheral, etc.).

The term "patient in need of such treatment and at risk of a thrombotic cardiovascular event" means a patient in need of both treatment for a cyclooxygenase-2 mediated disease and also at risk of a thrombotic cardiovascular event. One skilled in the art can diagnose a patient that is in need of treatment for a cyclooxygenase-2 mediated disease or condition and also at risk of suffering a thrombotic cardiovascular event. For example, such a patient may be a patient over the age of 50 with osteoarthritis and with a previous myocardial infarction. Other risk factors for a thrombotic cardiovascular event include hypertension, hypercholesterolemia, diabetes mellitus, chronic renal impairment, smoking, and any prior personal or family history of such an event. Administration of the drug combination to the patient includes both self-administration and administration to the patient by another person.

The terms "inhibitor of cyclooxygenase-2", "cyclooxygenase-2 selective inhibitor" and "COX-2 inhibitor" as used herein embrace compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. Employing the human whole blood COX-1 assay and the human whole blood COX-2 assay described in C. Brideau et al, Inflamm. Res. *45*: 68-74 (1996), herein incorporated by reference, preferably, the compounds have a cyclooxygenase-2 IC_{50} of less than about 2 μM in the human whole blood COX-2 assay, yet have a cyclooxygenase-1 IC_{50} of greater than about 5 μM in the human whole blood COX-1 assay. Also preferably, the compounds have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 10, and more preferably of at least 40. The resulting selectivity may indicate an ability to reduce the incidence of common

NSAID-induced side effects, especially erosions and ulceration of the upper gastrointestinal mucosa.

Examples of cyclooxygenase-2 selective inhibitors include rofecoxib (VIOXX®, see U.S. Patent No. 5,474,995, hereby incorporated by reference in its entirety), etoricoxib (ARCOXIA™ see U.S. Patent No. 5,861,419, hereby incorporated by reference in its entirety), celecoxib (CELEBREX®, see U.S. Patent No. 5,466,823, hereby incorporated by reference in its entirety), valdecoxib (see U.S. No. 6,633,272, hereby incorporated by reference in its entirety), parecoxib (see U.S. No. 5,932,598, hereby incorporated by reference in its entirety), COX-189 (Novartis), BMS347070 (Bristol Myers Squibb), tiracoxib or JTE522 (Japan Tobacco), ABT963 (Abbott), CS502 (Sankyo) and GW406381 (GlaxoSmithKline).

The term "amounts that are effective to treat" is intended to mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, a system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. The term also encompasses the amount of a pharmaceutical drug that will prevent or reduce the risk of occurrence of the biological or medical event that is sought to be prevented in a tissue, a system, animal or human by a researcher, veterinarian, medical doctor or other clinician. The inhibitor of cyclooxygenase-2 may be administered at a dosage level up to conventional dosage levels for NSAIDs. Suitable dosage levels will depend upon the antiinflammatory effect of the chosen inhibitor of cyclooxygenase-2, but typically suitable levels will be about 0.001 to 50 mg/kg per day, preferably 0.005 to 30 mg/kg per day, and especially 0.05 to 10 mg/kg per day. The compound may be administered on a regimen of once or twice per day.

The term "amount effective to reduce the risk of" means the amount of a pharmaceutical drug that will prevent or reduce the risk of occurrence of the biological or medical event that is sought to be prevented in a tissue, a system, animal or human by a researcher, veterinarian, medical doctor or other clinician. Aspirin is administered at a dose of about 30 mg to about 1 g once every two to seven days, preferably at a dose of about 80 mg to about 650 mg.

An embodiment of the invention encompasses the above method wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of: rofecoxib, etoricoxib, celecoxib, valdecoxib, COX-189, BMS347070, tiracoxib, ABT963, CS502 and GW406381. A further embodiment of the invention encompasses the above method wherein the cyclooxygenase-2 selective inhibitor is

rofecoxib. Within this embodiment is encompassed the above method wherein rofecoxib is administered on a once or twice daily basis at a dose of about 12.5 mg or about 25 mg. Another embodiment of the invention encompasses the above method wherein the cyclooxygenase-2 selective inhibitor is etoricoxib. Within this embodiment is encompassed the above method wherein rofecoxib is administered on a once or twice daily basis at a dose of about 60 mg, 90 mg or about 120 mg. Another embodiment of the invention encompasses the above method wherein the cyclooxygenase-2 selective inhibitor is celecoxib. Within this embodiment is encompassed the above method wherein celecoxib is administered on a once or twice daily basis at a dose of about 100 mg or about 200 mg. Another embodiment of the invention encompasses the above method wherein the cyclooxygenase-2 selective inhibitor is valdecoxib. Within this embodiment is encompassed the above method wherein valdecoxib is administered on a once or twice daily basis at a dose of about 10 mg or about 20 mg.

An embodiment of the invention encompasses the above method wherein the cycloxygenase-2 selective inhibitor is administered orally on a once daily basis. Another embodiment of the invention encompasses the above method the cycloxygenase-2 selective inhibitor is administered orally on a twice daily basis.

An embodiment of the invention encompasses the above method wherein the cycloxoygenase-2 selective mediated disease or condition is osteoarthritis. Another embodiment of the invention encompasses the above method wherein the cycloxoygenase-2 selective mediated disease or condition is rheumatoid arthritis. Another embodiment of the invention encompasses the above method wherein the cycloxoygenase-2 selective mediated disease or condition is chronic pain.

In another embodiment, the invention encompasses the above method wherein aspirin is administered at a dose of about 30 mg to about 1 g. For purposes of this specification the term "unit dose" or when aspirin is indicated to be dosed "once every three to seven days" means the indicated amount is administered at the time of dosing rather than the amount taken on average over a prolonged interval. For example a dose of 325 mg taken every 3 days delivers approximately 758 mg per week, but the dose administered every third day or unit dose is 325 mg. Within this embodiment is encompassed the above method wherein aspirin is administered at a dose of about 80 to about 650 mg. Also within this embodiment is encompassed the above method wherein aspirin is administered at a dose of about 81 mg and wherein aspirin is administered at a dose of about 325 mg.

The invention encompasses the above method wherein aspirin is orally administered once every two days. The invention further encompasses the above method wherein aspirin is orally administered once every three days. The invention further encompasses the above method wherein aspirin is orally administered once every four days. The invention further encompasses the above method wherein aspirin is orally administered once every five days. The invention further encompasses the above method wherein aspirin is administered once every six days. The invention further encompasses the above method wherein aspirin is orally administered once every seven days.

In another embodiment, the invention encompasses a kit comprising a cyclooxygenase-2 selective inhibitor for oral administration on a once-daily or twice-daily basis and aspirin for oral administration once every two to seven days. For example, the kit may comprise a sequenced means of presenting the medication to the patient, such as a calendar pack, in which patients will be instructed to take either one or two tablets in a predefined order. Aspirin may either be provided as a separate tablet copackaged to be taken at the same time as the cycloxoygenase-2 selective inhibitor or, alternatively, within a single tablet that contains both active moieties.

For example, the kit may comprise a calendar pack wherein the patient is instructed to take a cyclooxygenase-2 selective inhibitor once a day, except every third, fourth, fifth or seventh day wherein the patient is instructed to take aspirin and the cycloxygenase-2 selective inhibitor as a single tablet. In another example, the kit may comprise a calendar pack wherein the patient is instructed to take a cyclooxygenase-2 selective inhibitor once each day, while every third, fourth, fifth or seventh day the patient is instructed to concomitantly take aspirin that is copackaged with the cycloxygenase-2 selective inhibitor.

In another embodiment, the invention encompasses the above kit wherein the medication is presented to the patient in a predefined sequenced order. Within this embodiment is encompassed the above method wherein the medication is presented to the patient as a calendar pack.

The invention also encompasses the above kit wherein the cyclooxygenase-2 selective inhibitor and aspirin are provided as a unit dosage for administration on the same day. A "unit dosage form" means that both active moieties are combined together in the same pharmaceutical formulation. In another embodiment, the invention encompasses the above kit wherein the cyclooxygenase-2

selective inhibitor and aspirin are provided as separate dosage forms for concomitant administration on the same day.

In a further embodiment, the invention encompasses the above kit wherein the cyclooxygenase-2 selective inhibitor is rofecoxib. Within this embodiment is encompassed the above kit wherein rofecoxib is provided for administration on a once daily basis at a dose of about 12.5 mg or about 25 mg.

In another embodiment, the invention encompasses the above kit wherein the cyclooxygenase-2 selective inhibitor is etoricoxib. Within this embodiment is encompassed the above kit wherein etoricoxib is provided for administration on a once daily basis at a dose of about 60 mg, 90 mg or about 120 mg. Another embodiment of the invention encompasses the above kit wherein the cyclooxygenase-2 selective inhibitor is celecoxib. Within this embodiment is encompassed the above kit wherein celecoxib is provided for administration on a once daily basis at a dose of about 100 mg or about 200 mg. Another embodiment of the invention encompasses the above kit wherein the cyclooxygenase-2 selective inhibitor is valdecoxib. Within this embodiment is encompassed the above kit wherein valdecoxib is provided for administration on a once daily basis at a dose of about 10 mg or about 20 mg.

The invention encompasses the above kit wherein aspirin is provided for administration once every two to seven days at a dose of about 30 mg to about 1 g. Within this embodiment is encompassed the above kit wherein aspirin is provided for administration once every two to seven days at a dose of about 80 mg to about 650 mg. Also within this embodiment is encompassed the above kit wherein aspirin is provided for administration once every two to seven days at a dose of about 81 mg. Also within this embodiment is encompassed the above kit wherein aspirin is provided for administration once every two to seven days at a dose of about 325 mg.

The present invention also encompasses a method for treating a chronic cyclooxygenase-2 mediated disease or condition and reducing the combined risk of death and nonfatal stroke in a human patient who has had ischemic stroke of transient ischemia of the brain due to fibrin platelet emboli and also in need of treatment for a chronic cyclooxygenase-2 mediated disease comprising orally administering to said patient a cyclooxygenase-2 selective inhibitor on a once or twice daily basis in an amount effective to treat the chronic cyclooxygenase-2 mediated disease or condition and orally administering to said patient aspirin once every two to seven days at a dose of about 30 mg to about 1 g.

The present invention also encompasses a method for treating a chronic cyclooxygenase-2 mediated disease or condition and reducing the combined risk of death and nonfatal myocardial infarction in a human patient with a previous myocardial infarction or unstable angina pectoris and also in need of treatment for a chronic cyclooxygenase-2 mediated disease comprising orally administering to said patient a cyclooxygenase-2 selective inhibitor on a once or twice daily basis in an amount effective to treat the chronic cyclooxygenase-2 mediated disease or condition and orally administering to said patient aspirin once every two to seven days at a dose of about 30 mg to about 1 g.

The present invention also encompasses a method for treating a chronic cyclooxygenase-2 mediated disease or condition and reducing the combined risk of death and nonfatal myocardial infarction in a human patient with chronic stable angina pectoris and also in need of treatment for a chronic cyclooxygenase-2 mediated disease comprising orally administering to said patient a cyclooxygenase-2 selective inhibitor on a once or twice daily basis in an amount effective to treat the chronic cyclooxygenase-2 mediated disease or condition and orally administering to said patient aspirin once every two to seven days at a dose of about 30 mg to about 1 g.

The invention encompasses a method for treating a chronic cyclooxygenase-2 mediated disease or condition and preventing a thrombotic cardiovascular event in a human patient in need of such treatment and prevention comprising orally administering to said patient a cyclooxygenase-2 selective inhibitor on a once or twice daily basis in an amount effective to treat the cyclooxygenase-2 mediated disease or condition and orally administering to said patient aspirin once every two to seven days in an amount effective to prevent the thrombotic cardiovascular event.

For purposes of this specification, references to the compounds of use in this invention are meant to also include the pharmaceutically acceptable salts.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring

substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N- dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2- dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

The compounds of use in this invention may have one or more chiral centers and the present compounds may occur as racemates, racemic mixtures and as individual diasteriomers or enantiomers with all such isomeric forms and mixtures thereof being included within the scope of this invention. Furthermore, some of the crystalline forms for compounds of the present invention may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds of the instant invention may form solvates with water or common organic solvents. Such solvates and hydrates, as well as anhydrous compositions, are encompassed within the scope of this invention. Some of the compounds described herein may contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

The COX-2 inhibitors that may be used with this invention encompass all pharmaceutically acceptable salt forms of the compounds. Examples of such salt forms of COX-2 inhibitors include but are not limited to salts derived from inorganic bases including aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When treating a patient following the methods of the present invention, aspirin and the cyclooxygenase-2 selective inhibitor may be administered on the same

day. Thus, the instant pharmaceutical combination comprising aspirin in combination with a COX-2 inhibitor includes administration of a single pharmaceutical dosage formulation which contains both aspirin and the COX-2 inhibitor, as well as administration of each active agent in its own separate pharmaceutical dosage formulation. Where separate dosage formulations are used, aspirin and the COX-2 inhibitor can be administered at essentially the same time, i.e., concurrently, or at separately staggered times, i.e., sequentially. The instant pharmaceutical combination is understood to include all these regimens. Administration in these various ways are suitable for the present invention as long as the beneficial pharmaceutical effect of aspirin and the COX-2 inhibitor are realized by the patient at substantially the same time. The dosage regimen utilizing aspirin in combination with COX-2 inhibitor is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt or ester thereof employed.

In the methods of the present invention, the active agents are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with a non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, modified sugars, modified starches, methyl cellulose and its derivatives, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and other reducing and non-reducing sugars, magnesium stearate, steric acid, sodium stearyl fumarate, glyceryl behenate, calcium stearate and the like. For oral administration in liquid form, the drug components can be combined with non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring and flavoring agents can also be incorporated into the mixture. Stabilizing agents such as antioxidants (BHA, BHT, propyl gallate, sodium ascorbate, citric acid) can also be added to stabilize the dosage forms. Other suitable components include gelatin, sweeteners, natural and synthetic gums such as acacia, tragacanth or alginates, carboxymethylcellulose, polyethylene glycol, waxes and the like.

The active drugs can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Active drug may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. Active drug may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinyl-pyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxy-ethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, active drug may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels.

The instant invention also encompasses a process for preparing a pharmaceutical composition comprising combining aspririn and the COX-2 inhibitor with a pharmaceutically acceptable carrier, as well as the pharmaceutical composition which is made by combining aspirin and the COX-2 inhibitor with a pharmaceutically acceptable carrier.

A therapeutically effective amount of aspirin and a COX-2 inhibitor can be used together for the preparation of a medicament useful for treating or preventing the disease or conditions herein. For example, the medicament may be comprised of a COX-2 inhibitor in combination with about 30 mg to 1 g of aspirin, or more particularly about 80 mg to about 650 mg of aspirin.

The instant invention also encompasses the use of aspirin for the preparation of a medicament for the combined use with a cyclooxygenase-2 inhibitor for use as provided by the present invention; and the use of a cyclooxygenase-2 inhibitor for the preparation of a medicament for the combined use with aspirin for use as provided by the present invention.

WHAT IS CLAIMED IS:

1. A method for treating a chronic cyclooxygenase-2 mediated disease or condition and reducing the risk of a thrombotic cardiovascular event in a human patient in need of such treatment and at risk of a thrombotic cardiovascular event comprising orally administering to said patient a cyclooxygenase-2 selective inhibitor on a once or twice daily basis in an amount effective to treat the cyclooxygenase-2 mediated disease or condition and orally administering to said patient aspirin once every two to seven days in an amount effective to reduce the risk of the thrombotic cardiovascular event.

2. The method according to Claim 1 wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of: rofecoxib, etoricoxib, celecoxib, valdecoxib, COX-189, BMS347070, tiracoxib, ABT963, CS502 and GW406381.

3. The method according to Claim 1 wherein the cyclooxygenase-2 selective inhibitor is rofecoxib.

4. The method according to Claim 3 wherein rofecoxib is administered on a once or twice daily basis at a dose of about 12.5 mg or about 25 mg.

5. The method according to Claim 4 wherein rofecoxib is administerd on a once daily basis.

6. The method according to Claim 1 wherein the cyclooxygenase-2 selective inhibitor is etoricoxib.

7. The method according to Claim 6 wherein etoricoxib is administered on a once or twice daily basis at a dose of about 60 mg, about 90 mg or about 120 mg.

8. The method according to Claim 1 wherein the cyclooxygenase-2 selective inhibitor is celecoxib.

9. The method according to Claim 8 wherein celecoxib is administered on a once or twice daily basis at a dose of about 100 mg or about 200 mg.

10. The method according to Claim 1 wherein the cyclooxygenase-2 selective inhibitor is valdecoxib.

11. The method according to Claim 10 wherein valdecoxib is administered on a once or twice daily basis at a dose of about 10 mg or about 20 mg.

12. The method according to Claim 1 wherein the cyclooxygenase-2 selective inhibitor is administered orally on a once daily basis.

13. The method according to Claim 1 wherein the cyclooxygenase-2 selective inhibitor is administered orally on a twice daily basis.

14. The method according to Claim 1 wherein the cyclooxygenase-2 selective mediated disease or condition is osteoarthritis.

15. The method according to Claim 1 wherein the cyclooxygenase-2 selective mediated disease or condition is rheumatoid arthritis.

16. The method according to Claim 1 wherein the cyclooxygenase-2 selective mediated disease or condition is chronic pain.

17. The method according to Claim 1 wherein aspirin is administered at a dose of about 30 mg to about 1 g.

18. The method according to Claim 17 wherein aspirin is administered at a dose of about 80 to about 650 mg.

19. The method according to Claim 18 wherein aspirin is administered at a dose of about 81 mg.

20. The method according to Claim 18 wherein aspirin is administered at a dose of about 325 mg.

21. The method according to Claim 1 wherein aspirin is orally administered once every two days.

22. The method according to Claim 1 wherein aspirin is orally administered once every three days.

23. The method according to Claim 1 wherein aspirin is orally administered once every four days.

24. The method according to Claim 1 wherein aspirin is orally administered once every five days.

25. The method according to Claim 1 wherein aspirin is orally administered once every seven days.

26. A kit comprising a cyclooxygenase-2 selective inhibitor for oral administration on a once or twice daily basis and aspirin for oral administration once every two to seven days.

27. The kit according to Claim 26 wherein the medication is presented to the patient in a predefined sequenced order.

28. The kit according to Claim 27 wherein the medication is presented to the patient as a calendar pack.

29. The kit according to Claim 26 wherein the cyclooxygenase-2 selective inhibitor and aspirin are provided as a unit dosage for administration on the same day.

30. The kit according to Claim 26 wherein the cyclooxygenase-2 selective inhibitor and aspirin are provided as separate dosage forms for concomitant administration on the same day.

31. The kit according to Claim 26 wherein the cyclooxygenase-2 selective inhibitor is rofecoxib.

32. The kit according to Claim 31 wherein rofecoxib is provided for administration on a once daily basis at a dose of about 12.5 mg or about 25 mg.

33. The kit according to Claim 26 wherein the cyclooxygenase-2 selective inhibitor is etoricoxib.

34. The kit according to Claim 33 wherein etoricoxib is provided for administration on a once daily basis at a dose of about 60 mg, about 90 mg or about 120 mg.

35. The kit according to Claim 26 wherein the cyclooxygenase-2 selective inhibitor is celecoxib.

36. The kit according to Claim 35 wherein celecoxib is provided for administration on a once daily basis at a dose of about 100 mg or about 200 mg.

37. The kit according to Claim 26 wherein the cyclooxygenase-2 selective inhibitor is valdecoxib.

38. The kit according to Claim 37 wherein valdecoxib is provided for administration on a once daily basis at a dose of about 10 mg or about 20 mg.

39. The kit according to Claim 26 wherein aspirin is provided for administration once every two to seven days at a dose of about 30 mg to about 1 g.

40. The kit according to Claim 39 wherein aspirin is provided for administration once every two to seven days at a dose of about 80 mg to about 650 mg.

41. The kit according to Claim 40 wherein aspirin is provided for administration once every two to seven days at a dose of about 81 mg.

42. The kit according to Claim 40 wherein aspirin is provided for administration once every two to seven days at a dose of about 325 mg.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/38376

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 9/20, 9/127, 31/135, 31/415, 31/44
US CL : 424/464, 450; 514/349, 352, 406, 646

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/464, 450; 514/349, 352, 406, 646

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST/BRS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01/91750 A1 (PHARMCIA CORPORATION) 06 December 2001 (06.12.2001), the entire document.	1-42
Y, P	US 2002/0071857 A1 (KARARLI et al) 13 June 2002 (13.06.2002), the entire document	1-42

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 February 2003 (10.02.2003)	11 MAR 2003
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Simon J. Oh Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)